

Enhancing the Modeling of PFOA Pharmacokinetics with Bayesian Analysis



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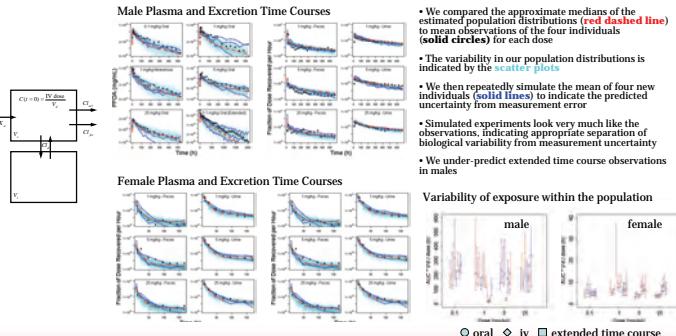
Abstract

The detail sufficient to describe the pharmacokinetics (PK) for perflurooctanoic acid (PFOA) and the methods necessary to combine information from multiple data sets are both subjects of ongoing investigation. Bayesian analysis provides tools to accommodate these goals. We examined the results of a series of experiments (Kemper 2003) that observed the concentration of PFOA in male and female adult rats. For some subjects plasma concentration was observed over time, while for others feces and urine were collected. Assuming that the PK parameters for each individual were drawn from the same biologically-varying population, we jointly analyzed both types of data. This hierarchical approach allowed us to estimate the contributions of uncertainty due to measurement error and actual biological variability.

We performed a Bayesian analysis using Markov Chain Monte Carlo. Since PFOA excretion is known to be sexually dimorphic in rats, we analyzed the male and female data separately. The distributions of integrated plasma concentration (AUC) varied significantly because the clearance is much higher in females ($35.6 \pm 9.2 \text{ mL/kg/h}$) than in males ($0.81 \pm 0.24 \text{ mL/kg/h}$).

Starting from a one-compartment PK model with separate clearances to urine and feces, we incrementally expanded the model using Bayesian measures to assess if the expansion was supported by the data. Including excretion data initially decreased certainty in the AUC compared to an analysis using plasma data only. Allowing a third, unspecified clearance improved agreement and increased certainty when all the data was used. However, the PFOA cleared by this third route appeared too large to be experimentally plausible. Adding an additional PK compartment was supported by the data and reduced the unaccounted-for elimination to amounts comparable to the cage wash. Since we have established that the data require more complicated models, PBPK models may provide additional insights.

PFOA Pharmacokinetics in Male and Female Rats

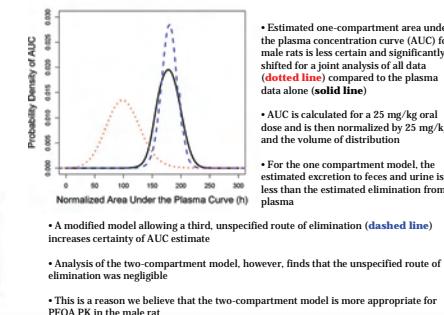


Motivation

- We are investigating the distribution and clearance of PFOA
- We are examining individual animal data from repeat measure studies of adult male and female Sprague-Dawley Rats (Kemper 2003)
- Initially interested in two types of data from studies:
 - PFOA plasma concentration time courses for five oral doses and one intravenous dose
 - PFOA material balance through fecal and urinary elimination for three oral doses
- We wish to estimate **pharmacokinetic parameters without prior knowledge**
- We would like to **treat all experiments as an ensemble** in order to estimate population parameters
- We want to use the **simpliest model** supported by the data
- Bayesian analysis using MCMC allows simultaneous estimates of distribution of all parameters and provides tools for model comparison
- A hierarchical statistical model allows separation of uncertainty and actual inter-individual variability of parameter values

Results

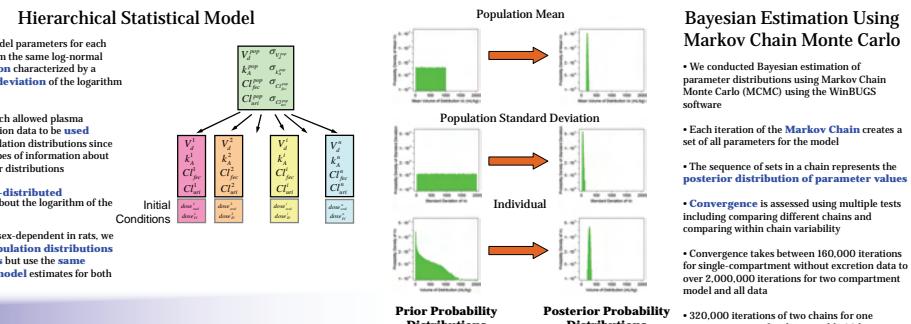
Estimates for Inappropriate Models Get Worse with More Data



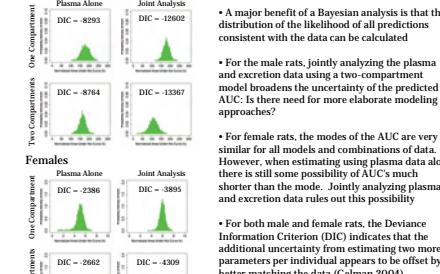
Methodology

Hierarchical Statistical Model

- We assume that the model parameters for each individual are drawn from the same log-normal **population distribution** characterized by a **mean** and a **standard deviation** of the logarithm of the parameters
- This population approach allowed plasma concentration and excretion data to be used **jointly** to estimate population distributions since they provide different types of information about the population parameter distributions
- We assumed **normally-distributed measurement error** about the logarithm of the concentration
- Since PFOA kinetics is sex-dependent in rats, we estimated **different population distributions** for males and females but use the **same measurement error model** estimates for both sexes



Bayesian Criteria for Model Selection



Conclusion

- We estimated pharmacokinetic parameters for PFOA in Sprague-Dawley rats **without prior knowledge** of values using **multiple types** of data sets
- For every parameter, we separately estimate measurement **uncertainty** and population **variability**
- The data support a two-compartment model over a one-compartment model for the pharmacokinetics of PFOA

References

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- Lunn, D. J., Thomas, A., Best, N., and Spiegelhalter, D., "WinBUGS -- A Bayesian modeling framework: Concepts, structure and extensibility," *Statistics and Computing*, **10**, 325-337 (2000)
- This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.